Plasma Cell Disorders and Dialysis-Dependent Renal Failure: Safety and Efficacy of Autologous Stem Cell Transplantation

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Approximately 20–40% of patients with plasma cell disorders have renal impairment at the time of diagnosis, and up to 2–3% of patients will require dialysis during their disease course [1, 2]. Patients who require dialysis are reported to have a poor prognosis. Although several studies have shown equivalent response rates to conventional chemotherapy in patients with mild to moderate renal insufficiency compared to those with normal renal function, the survival of myeloma patients with renal impairment is still significantly shorter. This can be attributed to an increased risk of early death, association of renal dysfunction with advanced disease, and also in part to reluctance in the use of intensive chemotherapy. Therefore, patients with dialysis-dependent renal failure are frequently considered unfit for high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) [3–8]. There are limited data about patients with dialysis-dependent renal failure undergoing ASCT. It is encouraging, however, that even in patients with severe renal failure, improvements in renal function following transplantation can be observed. However, this treatment approach was associated with higher rates of toxicity and transplant-related mortality [5–15]. We aimed to demonstrate that, in patients with plas-

ma cell disorders and dialysis-dependent renal failure, ASCT is feasible and can improve disease response.

We retrospectively analyzed our transplant database from 2004 to June 2017 to identify all myeloma and AL (light chain amyloidosis) patients who received ASCT while they were dialysis dependent. We identified 7 patients with advanced renal failure due to plasma cell disorder who required dialysis during ASCT. At diagnosis, patients received induction therapy according to the standard regimens used in plasma cell disorders. In the majority (6 out of 7 patients), bortezomib-based regimens were administered. Peripheral blood stem cells (PBSC) were mobilized using different mobilization factors: 2 patients with granulocyte colony-stimulating factor (lenograstim 5 µg/kg subcutaneous [sc] b.i.d. for 4 days), 4 patients with high-dose cyclophosphamide (CTX-HD) i.v. day 1 (1 patient 2 g/m², 3 patients 3 g/m²), and G-CSF (lenograstim 5 µg/kg/day sc day 4–9 then b.i.d. until apheresis collection has been completed), 1 patient with CTX-HD i.v. day 1 (2 g/m²), G-CSF (lenograstim 5 µg/kg/day sc day 4–9 then b.i.d. until hematopoietic stem cell [HSC] apheresis collection has been completed), and plerixafor (0.16 mg/kg/day sc after 10 days of G-CSF treatment until HSC apheresis col-

lection has been completed). Plerixafor was administered on demand because the peak CD34+ cell preapheresis count was less than 20 cells/µL. The patient required plerixafor dose escalation to 0.24 mg/kg/day with subsequent successful mobilization. No plerixafor-related toxicities were reported. A minimum of 2×10^6 CD34+ cells/kg were required to proceed to ASCT. The conditioning regimen for all patients consisted of melphalan (cumulative dose depending on age and clinical status). Patients received G-CSF 5 µg/kg sc daily from the day after PBSC infusion until an absolute neutrophil count >1,000/µL. Antiemetic prophylaxis was administered. Patients were routinely transfused for Hb <8 g/dL or PLT <20,000/µL. Neutrophil engraftment was defined as the first of 3 consecutive days on which the absolute neutrophil count exceeded 500/µL. Response and progression were measured according to the “International Myeloma Working Group consensus criteria for response and minimal residual assessment in multiple myeloma” and according to the 2011–2012 guidelines for amyloidosis from the University of Pavia. Response to ASCT was assessed at approximately 100 days post-ASCT. Toxicity was measured according to the Common Terminology Criteria for Adverse Events version 4.0.

Table 1. Patient characteristics

Median age at diagnosis, years	59 (43–66)
Median age at ASCT, years	60 (43–67)
<i>Sex</i>	
Male	4
Female	3
<i>Histology</i>	
Light chain κ myeloma	1
IgG λ myeloma	2
AL amyloidosis	1
Light chain λ myeloma	1
IgG κ myeloma	1
IgA λ myeloma	1
Multiple myeloma and concomitant AL amyloidosis	2
<i>DSS</i>	
I	1
II	0
III	4
B sign/symptoms +	4
Unknown	2
Median time from diagnosis to ASCT, months	15 (8–19)
<i>Dialysis requirements</i>	
1–2 times per week before ASCT	3
≥ 3 times per week before ASCT	4
Median CD34+ PBSC mobilized, $\times 10^6/\text{kg}$	3.1
<i>Induction regimen</i>	
Bortezomib-based regimens	6
Other	1
<i>Melphalan dose</i>	
200 mg/m^2	1
$< 200 \text{ mg}/\text{m}^2$	6
Median neutrophil engraftment time, days	10
<i>Induction response</i>	
CR/VGPR	3
PR	4
<i>ASCT response at 100 days</i>	
CR/VGPR	4
PR	2
Unknown	1
<i>Maintenance therapy post-ASCT</i>	
Yes	1
No	6

ASCT, autologous stem cell transplantation; DSS, Durie Salmon Staging System; PBSC, peripheral blood stem cells; CR, complete response; VGPR, very good partial response; PR, partial response.

Treatment-related mortality was defined as any death not related to relapse, within approximately 100 days of transplant and at 6 and 12 months after the transplant. Overall survival was calculated from the date of ASCT to the date of death due to any cause, with living patients censored on the last follow-up date. Progression-free survival was calculated from the date of ASCT to the date of progression or date of death; patients alive without progression were censored on the date of last follow-up.

The patient characteristics are outlined in Table 1. Six patients were receiving hemodialysis and 1 was receiving peritoneal dialysis. In 1 case a renal biopsy diagnosed renal AL amyloidosis. In the other 6 patients we assumed that the causes of renal failure were light-chain cast nephropathy and/or light-chain deposition disease, excluding other comorbidities as causes of renal impairment and considering the concomitant increasing of the monoclonal protein and the renal impairment onset. One patient received full-dose melphalan ($200 \text{ mg}/\text{m}^2$) as the conditioning regimen; 1 received a reduced melphalan dose of $140 \text{ mg}/\text{m}^2$. The other 5 patients received a nonmyeloablative conditioning regimen with a melphalan dose of $100 \text{ mg}/\text{m}^2$ ($n = 4$) or $75 \text{ mg}/\text{m}^2$ ($n = 1$). The median number of PBSC infused was 3.1×10^6 cells/kg (range $2.14\text{--}4.41 \times 10^6$ cells/kg). The median time to neutrophil engraftment was 10 days. Bedside dialysis treatment was done on the day before and on the day after melphalan administration. Hemodialysis treatment was always done at the bedside during the period of neutropenia post-ASCT. Treatment-related mortality was 0%. At the time of the last follow-up, 4 patients were still alive without disease progression and 3 were lost to follow-up. The nonhematologic toxicities (all grades) were mucositis, febrile neutropenia, delirium, and atrial dysrhythmias. Documented infections included *Staphylococcus epidermidis* and *Enterobacter cloacae* bacteremia ($n = 2$, only 1 microbiologically documented infection was catheter related), and *Clostridium difficile* diarrhea ($n = 1$). One patient developed neutropenic enterocolitis. The 100-day and the 6, and 12-month treatment-related mortality was 0%.

The overall response rate was 100%, including: complete response (CR), $n = 2$; very good partial response (VGPR), $n = 2$, and partial response (PR), $n = 2$. All the patients confirmed or improved their previ-

Patient	Response before ASCT	Response after ASCT
1	VGPR	VGPR
2	PR	CR
3	CR	CR
4	VGPR	Not evaluable
5	PR	VGPR
6	PR	PR
7	PR	PR

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Fig. 1. Responses before and after ASCT.

ous response after ASCT treatment, as listed in Figure 1. One patient reduced peritoneal dialysis requirements from 6 times a week to 3 times a week after ASCT. After a median follow-up of 2.1 years (7 months to 5 years), no patients have progressive disease.

Renal failure in myeloma patients is a frequently encountered problem. The prognosis is generally poor and these patients are often considered unfit for high-dose therapy and ASCT. We did not observe any impediment to hematopoietic

progenitor cell mobilization by dialysis. All patients in our study were able to collect a sufficient number of PBSC for ASCT. This is in line with our historical experience with nondialysis patients. Though our study is retrospective in nature and with a small sample size, we are able to demonstrate that in patients with plasma cell disorders and dialysis-dependent renal failure, ASCT is feasible and can improve disease response. Dialysis should not constitute a parameter for exclusion from high-dose therapy and ASCT. Prospective

randomized trials in patients with severe renal failure are mandatory in order to further optimize treatment-related toxicity and improve the outcome of this frequently neglected group of patients.

Disclosure Statement

The authors declare no conflicts of interest.

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